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A Systematic Review on Eye as a Biomarker and an Application of Quantum Neural Network

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Abstract

Artificial intelligence approaches, such as deep learning models, can be utilized for image analysis tasks such as disease prediction from retinal images. In addition to eye disorders, retinal images may help identify a variety of non-eye ailments, including diabetes, hypertension, chronic kidney disease, anemia, Alzheimer's and Parkinson's disease, and other conditions associated with age and gender. This research aims to establish the eye as a biomarker to diagnose non-ocular systemic diseases by applying quantum neural networks to diagnose diabetic retinopathy using fundus retinal images. To do so, we assess past research on recognizing non-ocular disorders utilizing the power of AI algorithms and retinal images. This study presents a systematic review involving the organization, summarization, and analysis of 51 full-length articles chosen by the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) model for paper selection. Significant and intriguing discoveries indicate that retinal images are widely utilized to diagnose diseases such as diabetes and hypertension, where the thickness of the blood vessels inside the retina is dramatically altered. However, research is still ongoing to establish a baseline for some disorders. AI techniques diagnose other diseases, i.e., anemia, Alzheimer's, Parkinson's, and kidney disease. Our review shows that non-ocular diseases can be diagnosed using only retinal images. Hence, the eye is a biomarker, and, unquestionably, it is a significant discovery for medical purposes. For this, the time and cost of diagnosis could be drastically reduced, and only a retinal snapshot would be required to detect a collection of chronic diseases.

Categories: AI applications, Quantum Computing, Image Processing and Analysis
Keywords: biomarker discovery, eye study, retinopathy, systematic review, artificial intelligence and image processing

Introduction And Background

A biomarker is a diagnostic sign that can be objectively measured and evaluated to determine if someone has or is predisposed to a disease. Biomarkers can measure normal biological processes, pathogenic processes, pharmacological responses to therapeutic interventions, or any other measurable diagnostic indicator [1,2]. Examples include expression profiles of messenger RNA, circulating tumor cells, DNA, proteins, proteomic patterns, lipids, metabolites, imaging techniques, and electrical signals. Urine, blood, and tissues are all potential sources for these signals or biomarkers [3]. The use of biomarkers has improved after evaluating artificial intelligence (AI) technologies. Today, various images (brain, retina, organs, skin, facial, etc.) and signals (brain, ECG, EEG, heart rate, respiratory rate, etc.) are also sources of disease detection indicators. So, is the eye going to be a new biomarker for disease detection? In this article, we will explain it.

Some disorders not related to the human eye can also be detected with retinal imaging. Many blood vessels are in the retina, and a thin layer of tissue is in the back of the eye [4]. These blood vessels can show how other parts of the body are doing. Studies have shown that retinal imaging can be used to detect hypertension, which can damage the retina's blood vessels. In some circumstances, the European Guidelines (2013) for diagnosing and managing hypertension continue to call for fundus inspection [1]. Hypertensive retinopathy is a disease that affects the blood vessels in the eye's retina. High blood pressure that is uncontrolled and persists for a long time is the cause. The retina, which is made up of light-sensitive cells in the back of the eye, is in charge of sending vision information to the brain [5]. It has no signs until the late stages, when you may start to lose sight or have other problems [5]. Retinal imaging can also find problems with the heart, such as atherosclerosis and blood clots [6]. Research has also employed retinal imaging to diagnose non-ocular disorders like Alzheimer's disease, diabetic nephropathy (a kidney disease related to diabetes), sleep apnea, and cancer [7]. However, these studies are still ongoing, and the diagnostic precision and clinical value of these imaging methods for diseases other than eye conditions have not yet been established.

Yet, the eye has the potential to serve as a biomarker. The idea is that AI technologies are overly effective

at image analysis, including processing, segmentation, registration, and recognition. Since 2012, significant advances have been made in the ability to represent models and the processing power of graphics processing units [8]. High-performance computing is becoming increasingly demanding in computer science, and a vast amount of image and multimedia data is now available. Therefore, imaging is a well-established biomarker, whereas retinal image analysis is a relatively recent area of research. This number is relatively small since retinal photographs are already used to diagnose some diseases. However, if the datasets are available, many diseases could be identified using deep learning algorithms.

Few systematic review studies have been done based on ocular retinal images with AI techniques like machine learning and deep learning algorithms. Betzler et al. [7] worked with an article that attempted to detect age, sex, smoking, alcohol status, body composition factors, cardiovascular disease (CVD), hematological parameters, renal disease, neurodegenerative disease, metabolic disease, and hepatobiliary disease. They mainly focused on deep learning models with three types of images as inputs (retinal optical coherence tomography [OCT], fundus, and external eye images). There are limitations on the number of searched documents and the methods used; the procedure was not adequately described in the paper. In addition, using ophthalmic imaging to predict systemic disease necessitates the availability of accurate data and the collaboration of clinicians. Reducing barriers to accessing ophthalmic imaging datasets, such as cost, time, usability, and quality, is possible. Another study by Peng et al. [9] reviewed 33 articles, including cardiovascular, central nervous system, renal dysfunction, and hepatological diseases. This study aims to present a comprehensive overview of the available data and real-world uses of AI in eye image processing to find systemic diseases.

Therefore, after the above discussion, there are some research questions: i) Are AI models capable of diagnosing non-ocular diseases such as Alzheimer's, chronic kidney disease, diabetes, hypertension, anemia, and coronary artery disease using retinal images? ii) If so, what images are appropriate, and what model performs best? iii) Which non-ocular systematic diseases have been analyzed more, and which diseases need more research? Furthermore, we have set some aims for finding the analytical results: i) Define some keywords and phrases to search the research articles and find those articles from various repositories. ii) Use the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) model for article selection, inclusion, exclusion, and final study design. iii) Structure the analytical results from the study and present them in meaningful ways. iv) Give some references of publicly available datasets of those diseases for further research.

Our study investigated eye images, specifically retinal photographs, as a biomarker to diagnose non-eye diseases. For this purpose, we evaluated articles from 2012 on machine learning- and deep learning-based research on six diseases (using retinal images), including age and gender prediction (because graphics processing units have improved since 2012 [8]). We have included possible diseases, including diabetes, chronic kidney disease, Alzheimer's disease, coronary artery disease, anemia, and hypertension. Furthermore, we tried to gather a compendium of public ophthalmic imaging datasets to aid a future research dimension. The second target is applying a quantum neural network (QNN) model to fundus retinal images to diagnose diabetic retinopathy (DR), an example of using AI and quantum computing mechanisms. The main reason behind the application of quantum computing for retinal image analysis is to use the power of complex data handling and pattern recognition.

After evaluating 51 articles, we determined that some disease datasets (retinal images) are publicly accessible while others are not. We also discovered that researchers focused more on some diseases, whereas the literature on other diseases was scarce. The main contributions of this study are as follows:

• To establish the eye as a biomarker for disease diagnosis.

• To find a time- and cost-effective diagnosis system.

• A systematic review of six distinct disease-related articles employing retinal scans and AI algorithms.

• Organize and explain existing machine learning- and deep learning-based analytical articles that use retinal images as input and diagnose corresponding diseases.

• Find the application of the state-of-the-art trending AI algorithms and their performances to help the ophthalmologist with decision-making and give a comprehensive reference for the future direction of research in this field.

• For proof, apply the QNN model to diagnose DR using fundus images.

In general, we have reviewed articles to diagnose various disorders, including the literature related to age and gender.

Review

Methods

Study Selection Process

To conduct this study, we first examined a database of scholarly publications on using deep learning and machine learning models to assess retinal images. We then conducted a systematic review of the subject. We pursued the PRISMA [10] for this systematic review. In Figure *1*, we illustrate our search results.

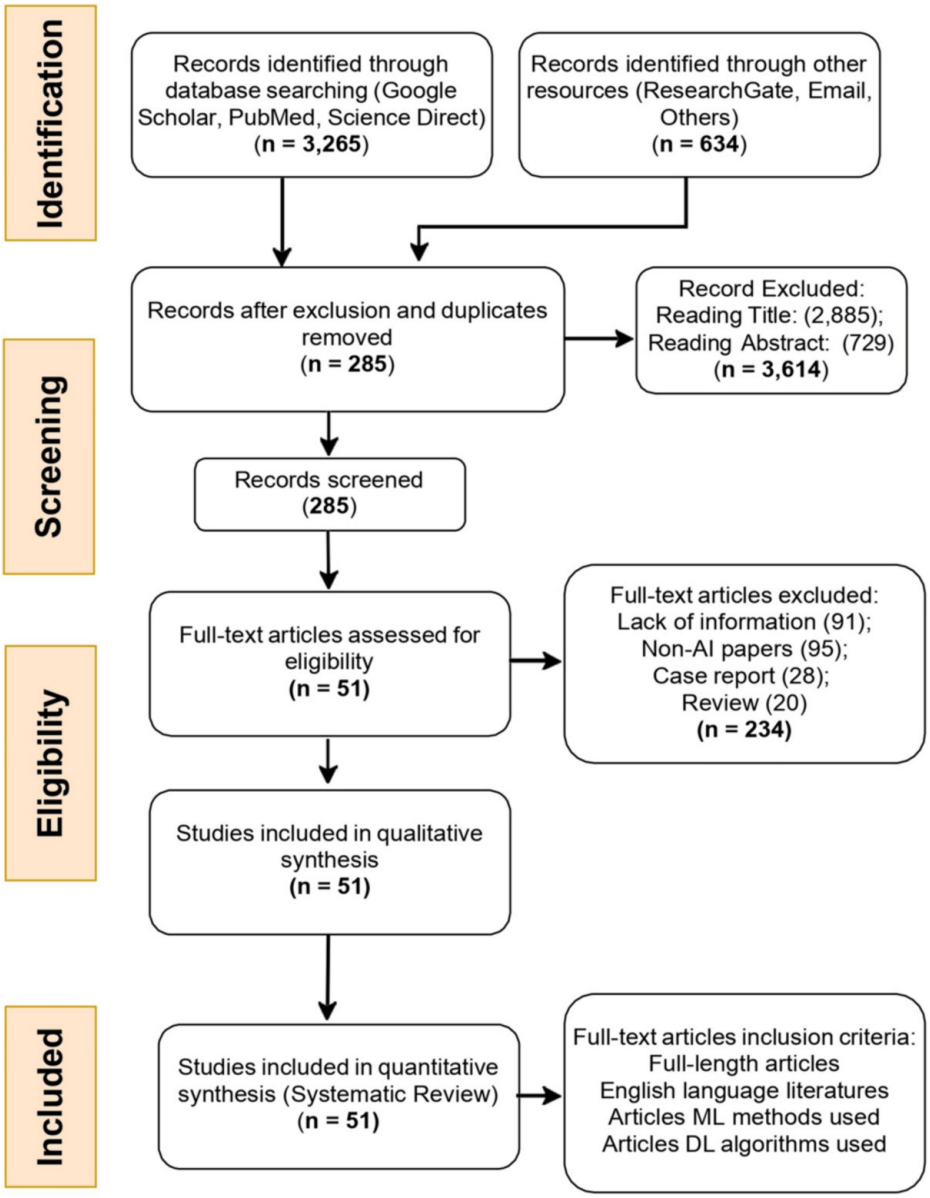

FIGURE 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for our analysis

DL, Deep Learning; ML, Machine Learning

In this systematic review study, we have collected publications from multiple repositories, such as Google Scholar, PubMed, Science Direct, and ResearchGate's public and private articles, and have requested authors' articles. The PRISMA paradigm was utilized for the selection of articles. It was separated into four sections, as seen in Figure *1*. The first section was titled Identification, in which 3,265 article records were found by searching Google Scholar, PubMed, and ScienceDirect databases. In other repositories, such as ResearchGate or emails to authors, 634 articles were discovered. During this stage, a total of 3,899 items were identified. The second phase, screening, excludes several papers after reading only their titles and abstracts. We removed 2,885 articles after the title and 729 articles after the abstract. We rejected 3,614

items based on this criterion. Therefore, after this step, only 285 articles remained. The third step was eligibility, and in this step, we also excluded several articles due to lack of information (n = 91), articles not related to AI (n = 95), case reports (n = 28), and review articles (n = 20) after reading and reviewing the entire document. After this stage, there were only 51 articles left for qualitative synthesis analysis. In the final phase, titled Included, the remaining (n = 51) articles were included based on the availability of full-text literature in English, and articles were analyzed using deep learning and machine learning algorithms.

Search Strategy and Inclusion Criteria

Digital bibliography searches were executed in PubMed and Web of Science for this narrative review on February 2, 2025. Google Scholar was used to do a deeper search to find any papers that had been skipped. Articles that used AI models to process ocular image data to diagnose diseases other than ophthalmology problems were included. Our search criteria were divided into two sections. First, we conducted a literature search using keywords such as "fundus photos," "retinal images," "optical coherence tomography," "optical coherence tomography angiography," and "eye images" to find articles based on ocular images. Second, we searched for systemic disorders, such as "diabetes," "Alzheimer's," "cardiovascular," "CKD," "hypertension," "kidney," "cognitive problems," "age and gender," "stress," "anemia," and "coronary artery." Our methodological terms were "deep learning," "machine learning," "ensemble learning," "neural networks," and "artificial intelligence," since our review was mainly based on work related to AI. We merged the three terms for the final search. All articles considered were available in English and full text. Retrospective and cross-sectional papers were also included. Surveys, case reports, case series, reviews, instructions, statistical models, and studies on eye disease diagnosis were omitted. The AI technique was characterized as applying deep learning and machine learning algorithms while creating models based on ocular images.

Data Extraction

After reviewing the studies, we designed a data table with numerous features, such as the author's name and year of publication, research input ocular image type and size, AI model structure (deep learning, machine learning), validation information, disease category, and outcome details. Our review of 51 articles based on systemic disease, methodological approach, and study findings addressed preliminary results and findings narratively. Each study used a different type of AI model; hence, various evaluation criteria were used to categorize the model's performance, including accuracy, sensitivity, specificity, and area under the receiver operating curve (AUROC). Furthermore, R^2, P, and Mini Mental State Examination (MMSE) are used to assess the effectiveness of regression models.

Retinal Imaging Modalities Used as Inputs

Ophthalmology offers a variety of clinically helpful imaging modalities, including retinal fundus photography (RFP), OCT, and OCT angiography (OCT-A) [6]. After reviewing 496 papers, Khan et al. [11] summarized publicly accessible datasets for ophthalmological images, and 94 were finally found. The top three datasets were RFP, OCT or OCT-A, and external ocular photos. On the contrary, designing robust AI models requires significant data at suitable dimensions, which might be challenging to gather. In this systematic study, therefore, most RFP, OCT, or OCT-A images and external eye images (EEI) were used as inputs for AI models to predict non-ocular diseases.

Various types of retinal images hold different kinds of properties. The brief descriptions of the image types are as follows:

• Fundus: Fundus images are 2D projections of the fundus taken by a monocular camera. They are noninvasive and inexpensive compared to other types of eye scans, such as OCT images and angiographs, making them better suited for widespread screening [10].

• OCT: OCT is an advanced technique for taking high-resolution cross-sectional retinal imaging [12]. Through this OCT image, structural and detailed information about the retinal image's layered architecture can be found. Similar to ultrasound, this technique uses light instead of sound. It captures micrometer-scale images with only low-coherence light. Real-time cross-sectional and high-resolution imaging helps to detect and monitor different types of ophthalmology diseases [12].

• Other Images: A set of images (beyond fundus and OCT) has been used to diagnose eye or chronic diseases using AI. For example, hyperspectral retinal imaging (HRI) uses images of the palpebral conjunctiva (PC), EEI, and infrared iris images (III). High-resolution retinal images are captured at various wavelengths of light using a noninvasive imaging method called HRI. This makes it possible to see changes in the retina that might suggest conditions including glaucoma, DR, and age-related macular degeneration [13]. Photographs of the conjunctiva (the lining of the eyelids) are known as the PC. Conjunctivitis, allergic reactions, and eye infections are just some problems these images could help

diagnose [14]. Images of the eyes taken from the outside depict how they seem. The eyelids, sclera, and other exterior parts of the eye may all be examined using these images. They may also track the development of a corneal ulcer or eyelid growth over time. An iris image is any picture of the colored portion of the eye that was taken in infrared and may be utilized to diagnose disorders like iritis and uveitis that affect the eyes [15].

Quantum Neural Network

QNN is implemented for the diagnosis of DR due to their significant benefits in the processing of complex, high-dimensional data. The QNN model has the capability of finding the complex pattern and analysis of high-dimensional data with the superposition and entanglement features. These features are beneficial for diagnosing the DR with more precise classification. Some research showed the comparison between the traditional deep learning model and the QNN. Additionally, QNN has shown the ability to decrease the model complexity while sustaining the performance for deploying them in clinical or mobile-based applications. We have trained a dataset as an experiment on QNN for the diagnosis of DR. It proves that QNN is suitable and applicable for medical image analysis. So, we can adopt quantum computers for this kind of application. For comparison, we also trained the ResNet50 model.

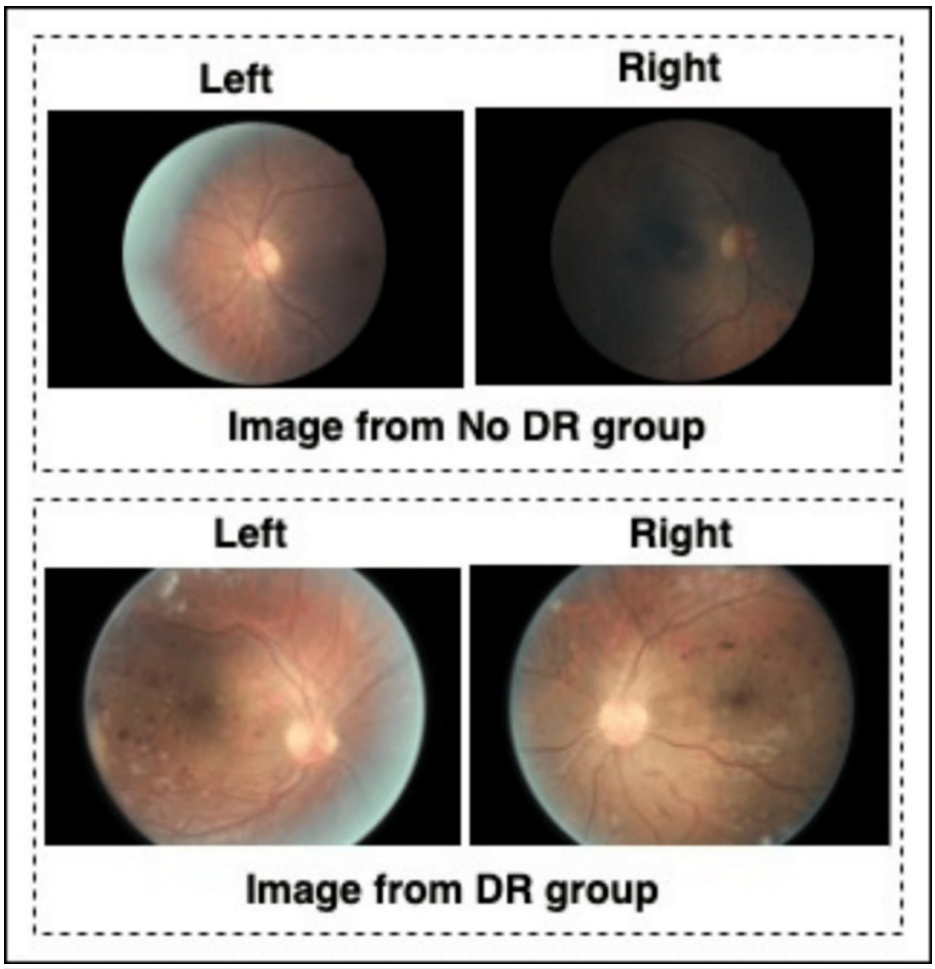

FIGURE 2: Sample retinal images (DR and non-DR)

DR, Diabetic Retinopathy

• Dataset: We have chosen one of the most used and trusted datasets for this analysis, APTOS 2019 [16]. We have taken 1,861 diabetic retinal images and 1,806 standard images. In the dataset, both left and right eye retinal images exist equally. Figure *2* shows the sample images.

• Image Processing: First, we reshaped the image's 224 × 244 × 3 size and then applied a Gaussian filter. The filtered images are directly fed into the QNN models. We also normalize the images and split the dataset. In the model training, we have split the images as follows: 70% for training, 20% for validation, and 10% for testing.

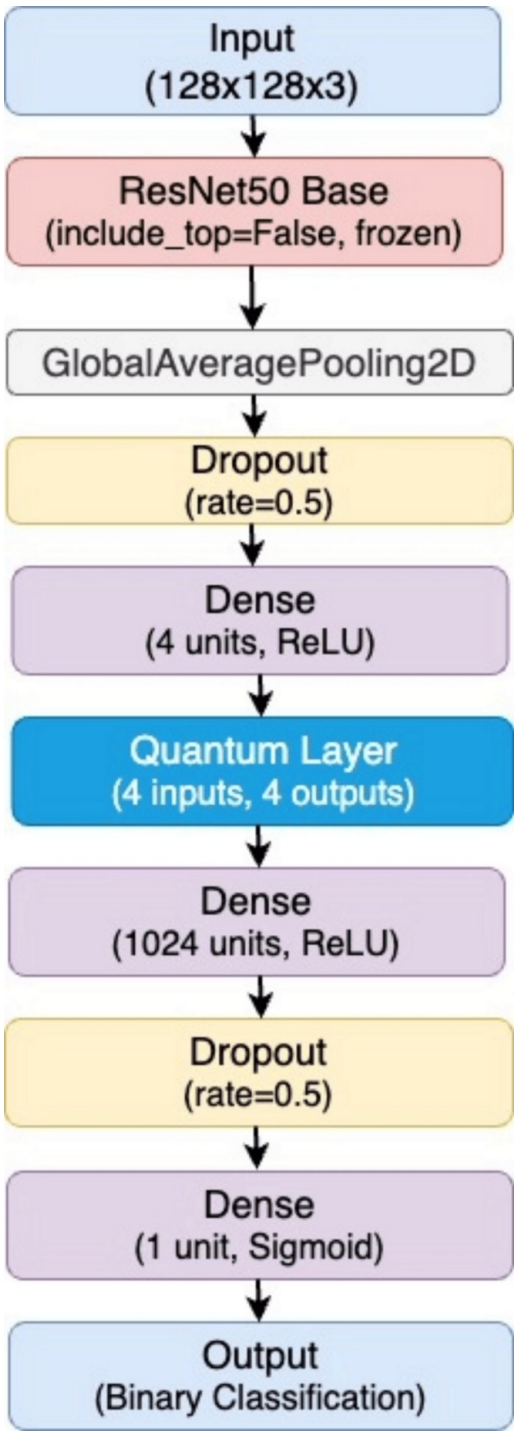

FIGURE 3: The architecture of the hybrid QNN model

QNN, Quantum Neural Network

• QNN Model: We used a hybrid QNN model in this analysis. The base model was ResNet50. The model architecture is shown in Figure *3*. Here, it is seen that, firstly, an input layer, then the base model layer ResNet50, and then a global average pooling layer 2D is used, then a dropout layer with rate 0.5, again a dropout layer with four units and ReLU activation, and the four-qubit quantum layer were added that can handle four inputs and four outputs. Then again, we placed the dense layer (1,024 units, activation ReLU), the dense layer (1 unit, activation sigmoid), and, finally, the output layer for binary classification.

Results

After reviewing the articles, we have seen that the authors have used a variety of machine learning and deep learning models, mainly neural networks. They have also utilized several evaluation metrics to

evaluate the results, i.e., accuracy, sensitivity, specificity, MMSE, AUC-ROC, R^2, and P value.

They mostly used OCT and fundus retinal images as training data, including some less commonly used image formats, i.e., retinal external photographs (RF), PC, EEI, and III. A brief representation of the performances of the various models in the previous works is shown in Table *1*. Most of the studies used AUC-ROC as an evaluation matrix and achieved 100% using fundus images [17], and all the works except two achieved above 80%. The second most used matrix is accuracy, which achieved a 100% accuracy score using fundus images and other papers [18]. Those who have used accuracy as an evaluation matrix also got above 80%, except in two analyses. The following popular matrices are sensitivity and specificity; those scores are also promising, above 80%, and sometimes they are nearly 100%. The MMSE, R^2, and P values are the less commonly used matrices. Only one paper used MMSE, another used P, and the other two articles used R^2. It is mentioned that the values of MMSE, R^2, and P are good enough in the corresponding studies. It is also observed that for disease diagnosis, the highest accuracy scores achieved are as follows: Alzheimer's disease - 92% (Cheung et al. [19]), anemia - 97% (Jain et al. [20]), hypertension - 99% (Sajid et al. [21]), age and gender prediction - 99% (Khalifa et al. [22]), and diabetes - 99% (Hacisoftaoglu et al. [23]).

Disease	Paper	Image	Accuracy	Sensitivity	Specificity	MMSE	AUROC	R^2	P
Alzheimer's disease	Cheung et al. [19]	Fundus	0.92	–	–	–	–	–	–
	Tian et al. [24]	Fundus	0.82	0.7	0.85	–	–	–	–
	Wisely et al. [25]	OCT	–	–	–	29.2	0.84	–	–
	Lemmens et al. [26]	OCT	–	–	–	–	0.79	–	–
	Nunes et al. [27]	OCT	–	88.7	–	–	–	–	–
Anemia	Wei et al. [28]	OCT	–	0.98	0.96	–	0.99	–	–
	Rim et al. [29]	Fundus	–	–	–	–	–	0.61	–
	Mitani et al. [30]	Fundus	–	–	–	–	0.87	–	–
	Chen et al. [31]	OCT	0.84	–	–	–	–	–	–
	Jain et al. [20]	PC	0.97	0.99	0.95	–	–	–	–
	Chen et al. [32]	PC	–	0.78	0.83	–	–	–	–
Coronary artery disease	Chang et al. [33]	Fundus	–	0.89	0.4	–	0.71	–	–
	Rim et al. [29]	Fundus	–	–	–	–	0.74	–	–
	Vaghefi et al. [34]	Fundus	–	–	–	–	–	–	<0.001
	Son et al. [35]	Fundus	–	–	–	–	0.82	–	–
	Poplin et al. [36]	Fundus	–	–	–	–	0.97	–	–
Chronic kidney disease	Akari et al. [37]	OCT	0.77	0.77	0.77	–	0.86	–	0.86
	Zhang et al. [38]	Fundus	–	–	–	–	0.93	–	–
	Rim et al. [29]	Fundus	–	–	–	–	–	0.38	–
	Sabanayagam et al. [17]	Fundus	–	–	–	–	1	–	–
	Kang et al. [39]	Fundus	–	–	–	–	0.81	–	–
Hypertension disease	Zhang et al. [40]	Fundus	–	–	–	–	0.77	–	–
	Dai et al. [41]	Fundus	–	–	–	–	0.99	–	–
	Sajid et al. [21]	Fundus	0.99	0.99	0.99	–	0.99	–	–
Age and gender	Korot et al. [42]	Fundus	0.79	0.84	0.72	–	–	–	–
	Munk et al. [43]	OCT	–	–	–	–	0.8	–	–
	Gerrits et al. [44]	Fundus	–	–	–	–	0.97	–	–
	Kim et al. [45]	Fundus	–	–	–	–	0.96	–	–
	Yamashita et al. [46]	Fundus	–	–	–	–	0.97	–	–

	Khalifa et al. [22]	EEI	0.99	–	–	–	–	–	–
	Poplin et al. [36]	Fundus	–	–	–	–	0.97	–	–
Diabetes disease	Saha et al. [18]	Fundus	1	1	1	–	–	–	–
	Hacisoftaoglu et al. [23]	Fundus	0.99	0.98	0.99	–	0.99	–	–
	Samant et al. [47]	III	0.9	0.97	0.99	–	–	–	–
	Aslam et al. [48]	OCT	0.49	–	–	–	0.8	–	–
	Lam et al. [49]	Fundus	0.75	–	–	–	–	–	–
	Alyoubi et al. [50]	Fundus	–	–	–	–	–	–	–
	Bellemo et al. [51]	Fundus	–	0.92	0.89	–	0.97	–	–
	Hsieh et al. [52]	Fundus	0.98	–	–	–	–	–	–
	Mohamed et al. [53]	Fundus	0.85	0.89	0.96	–	–	–	–
	Rego et al. [54]	Fundus	–	0.81	0.96	–	–	–	–
	Zang et al. [55]	OCT	–	–	–	–	0.96	–	–
	Bhuiyan et al. [56]	Fundus	–	0.99	0.98	–	0.99	–	–
	Dai et al. [57]	Fundus	–	–	–	–	0.97	–	–
	Oh et al. [58]	Fundus	0.83	–	–	–	0.92	–	–
	Heisler et al. [59]	OCT	0.92	–	–	–	–	–	–
	Elgafi et al. [60]	OCT	0.97	–	–	–	–	–	–
	Jacoba et al. [61]	Handheld	0.97	0.96	0.98	–	–	–	–
	Silva et al. [62]	UWF	0.64	0.72	0.63	–	–	–	0.15
	Gargeya et al. [63]	Fundus	–	0.94	0.98	–	0.97	–	–
	Wang et al. [64]	Fundus	–	0.91	0.81	–	0.94	–	–

TABLE 1: Summary of performances of the AI models for various disease detection

AUROC, Area Under the Receiver Operating Characteristic Curve; EEI, External Eye Images; III, Infrared Iris Images; MMSE, Mini Mental State Examination; OCT, Optical Coherence Tomography; PC, Palpebral Conjunctiva; UWF, Ultra-Widefield Imaging

The most commonly used image type is fundus/color fundus images, appearing in 36 studies, followed by OCT/OCT-A images, used in 10 studies. Except for those two types, they were used in only five studies.

The performance of the AI models is outstanding and promising. AI is also clinically applicable to practical applications in hospitals and clinics, but based on different imaging modalities and different dataset quality and size, the results differ. So, further research and extensive analysis will make the AI diagnosis system more robust and efficient. It could be a supplement for doctors as a tool for detecting, diagnosing, recognizing, and measuring disease prognosis using only retinal images. So, the eye could be a biomarker for disease diagnosis.

Performances of Neural Network Models to Diagnose DR

In this analysis, we trained two models: ResNet50 and hybrid QNN models. The performances are shown in Table *2*. Both models perform well, with above 90% accuracy, and all other evaluation scores like precision, recall, and AUC are also good. Though both models' performance matrices are similar, ResNet50 performed comparatively well. If we look at the testing loss, those scores are also good; for QNN, they are 0.18, and for ResNet50, they are 0.14.

Model	Accuracy	Precision	Recall	AUC	Loss
QNN	94.62	94.28	95.56	97.22	0.18
ResNet50	96.42	94.44	98.55	98.55	0.14

TABLE 2: Performances of the QNN model for DR detection

AUC, Area Under the Curve; DR, Diabetic Retinopathy; QNN, Quantum Neural Network

Discussion

In this survey, we have reviewed 51 full-length articles. These articles are classified according to diseases (diabetes, chronic kidney disease, Alzheimer's disease, coronary artery disease, anemia, hypertension), age, and sex. These articles have used OCT, fundus, or other types of images (HRI, PC, EEI, infrared eye images, OCT-A). The taxonomy of this study is based on the categorization of the articles, shown in Figure *4*.

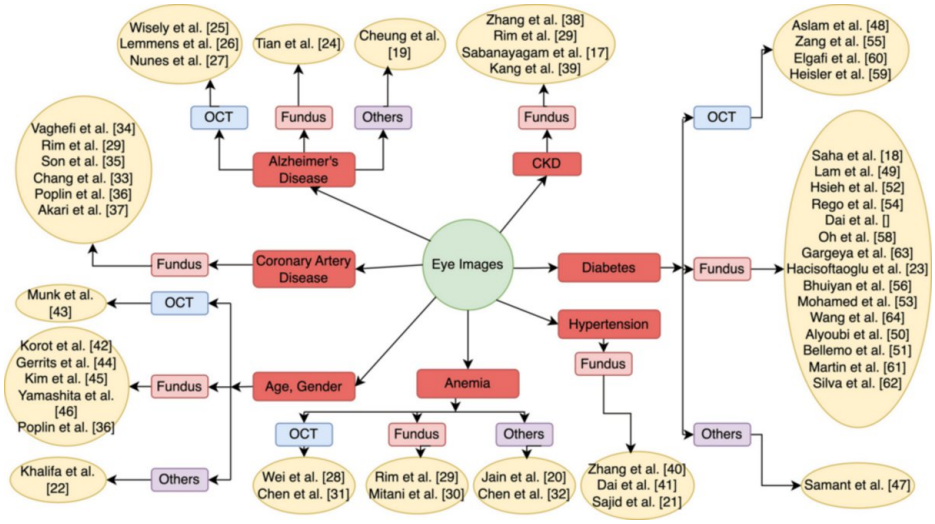

FIGURE 4: The taxonomy tree of all the articles is included with different categories

OCT, Optical Coherence Tomography; CKD, Chronic Kidney Disease

Eye as a Biomarker for the Detection of Neurodegenerative Diseases

Retinal neurovascular abnormalities also correspond to degenerative neurological diseases such as Alzheimer's disease, Parkinson's disease, and dementia. Numerous OCT investigations have shown that these changes include the loss of retinal ganglion cells and the thinned retinal layers caused by amyloid β-protein buildup in patients with Alzheimer's disease [65]. There is no straightforward method to detect Alzheimer's disease, in part because the condition is challenging to diagnose and sometimes requires costly and occasionally painful procedures that are uncommon outside of highly specialized healthcare settings. A set of previously done studies on Alzheimer's disease and comparative analysis is shown in Table *3*.

Paper	Input	AI Algorithms/Other Tests	Dataset Size	Type of Internal Validation	External Validation	Disease Covered	Outcomes	Reference Standard
Cheung et al. [19]	Retinal photographs	Bilateral DL	12,949 images	NA	Amyloid β burden	AD	Highest test accuracy 0.92, AUROC 0.91	Retrospective, multicentre, case-control study
Tian et al. [24]	Fundus photographs	SVM	122 images	5-fold cross-validation	Not Mentioned	AD	Accuracy 0.82, Sensitivity 0.79, Specificity 0.85	Clinical Diagnosis
Wisely et al. [25]	OCT and OCTA	CNN	284 eyes	Random split	NA	AD	MMSE 29.2 (control) vs. 21.9 (AD), AUC 0.84	Not Mentioned
Lemmens et al. [26]	HSRI and OCT	LDA	39 patients	Nested cross-validation	NA	AD	Highest AUROC 0.79	Not Mentioned
Nunes et al. [27]	OCT	ANOVA, SVM	75 patients	10-fold cross-validation	Not Mentioned	AD, PD	Sensitivity: Healthy 0.89, AD 0.80, PD 0.78	Clinical Diagnosis

TABLE 3: Comparison of works on Alzheimer's disease

AD, Alzheimer's Disease; ANOVA, Analysis of Variance; AUROC, Area Under the Receiver Operating Characteristic Curve; CNN, Convolutional Neural Network; DL, Deep Learning; HSRI, Hyperspectral Retinal Imaging; LDA, Linear Discriminant Analysis; MMSE, Mini Mental State Examination; OCT, Optical Coherence Tomography; OCTA, Optical Coherence Tomography Angiography; PD, Parkinson's Disease; SVM, Support Vector Machine

Cheung et al. [19] used a bilateral deep learning system to identify Alzheimer's disease-related dementia from retinal images. They developed a deep learning model that had 0.84 accuracy, 0.93 sensitivity, and 0.82 specificity and had an AUC-ROC of 0.93 for identifying Alzheimer's disease and dementia using 12,949 retinal images from 648 patients with the disease and 3,240 healthy subjects.

Their suggested retinal photograph-based deep learning model offers a straightforward, affordable, and labor-light solution method to identify possible patients with Alzheimer's disease with reasonable accuracy and sensitivity in community settings [19]. Tian et al. [24] took the initiative to assess the retinal vascularity and perform screenings for patients with dementia related to Alzheimer's. They could predict Alzheimer's disease using retinal fundus images, with encouraging results (accuracy 0.82, sensibility 0.79, specificity 0.85). Saliency maps revealed that the morphology of small retinal vessels was more critical than that of large vessels for the classification decision. This is consistent with earlier studies on the role of constriction of small cerebral arterioles in the pathogenesis of neurovascular dysfunction in Alzheimer's disease.

The RFP-based model was designed by Tian et al. [24], who described their automated multistage machine learning workflow, showcasing the first potential of machine learning-based retinal vascular analysis for detecting Alzheimer's disease. Most research in the present literature applied OCT-based models that predicted neurodegenerative disease. Using multimodal retinal pictures and patient data, Wisely et al. [25] created a convolutional neural network (CNN) to detect symptoms of Alzheimer's disease. A total of 284 eyes were used to train the model, which yielded a promising AUC of 0.84. They demonstrated that color maps of the inner plexiform layer of the ganglion cell were the most valuable prediction input.

The study by Lemmens et al. [26] used hyperspectral imaging and OCT to develop a classification model that distinguished patients with Alzheimer's disease from controls. In a linear discriminant classification model, hyperspectral and retinal nerve fiber layer thickness data were used to distinguish patients with Alzheimer's disease and controls, with an AUROC curve ranging from 0.67 to 0.79.

Furthermore, Nunes et al. [27] produced remarkable findings in predicting and identifying patients with Alzheimer's disease or Parkinson's disease using OCT images. However, due to the intensive preprocessing required by their research procedure, the final OCT data utilized to train the model differed significantly from the raw data commonly collected in clinical situations. For example, they used measurements of the thickness of the retinal layer to generate multivariate texture data. While this enhanced the discrimination ability of the model, it decreased the possibility that it could be translated for clinical use. Additionally, Kromer et al. [66] evaluated the clinical value of spectral-domain OCT (Spectralis OCT) to detect abnormalities of the retinal nerve fiber layer in people with Alzheimer's. They used the Kolmogorov-Smirnov and Student's t-test, not deep learning or machine learning models. For this disease, although all evaluation scores exceeded 80%, the training sample size was relatively small. Therefore, we recommend incorporating data from more diverse populations in future research and conducting external

validation to enhance the model's robustness and generalizability.

Eye as a Biomarker for the Detection of Anemia

A blood sample must be taken and tested to determine the hemoglobin level, which is crucial in diagnosing anemia. However, using a systematic approach, computers can automatically select patients with anemia for the screening process. A set of previously done studies on anemia and comparative analysis is shown in Table *4*. Wei et al. [28] investigated the deep learning-based anemia prediction problem using OCT images of retinal vessels. To increase productivity, they proposed a noninvasive end-to-end network (AneNet) to detect anemia and achieved a precision of 98.65%. Rim et al. [29] employed saliency maps to identify the area from which the deep learning algorithms would have predicted systemic biomarkers. Models trained with color fundus photographs to indicate age and sex predominantly highlighted the optic disc and retinal vessels. Models that predicted hematocrit, hemoglobin, systolic blood pressure (BP), and diastolic BP using attention masks focused on the characteristics of retinal vessels. Mitani et al. [30] determined that anemia may be diagnosed using machine learning algorithms based on RFP and explored the significance of different anatomical features to anemia by blurring and cropping the RFPs during training and validation. They showed that automated screening for anemia based on fundus images could be especially beneficial for diabetic patients who receive routine retinal imaging, for whom anemia increases the risks of morbidity and mortality. The research by Jain et al. [20] was intended to establish a noninvasive automated method for detecting anemia. They developed a new machine learning technique that uses an artificial neural network to identify anemic individuals based on photographs of the eye's conjunctiva. Computer vision methods were employed for preprocessing and feature extraction to standardize a noninvasive procedure. The model achieved 0.97 precision, 0.99 sensitivity, and 0.95 specificity of the created dataset.

Paper	Input	AI Structure/Other Method	Dataset Size	Type of Internal Validation	External Validation	Disease Covered	Outcomes	Reference Standard
Wei et al. [28]	OCT	Ane-Net	428 images	5-fold cross-validation	Not Mentioned	Hemoglobin (Anemia)	AUROC 0.9983, Sensitivity 98.38%, Specificity 95.94%	Clinical Measurement
Rim et al. [29]	Color Fundus	VGG-16	236,257 images	Random split	From four hospitals/repositories	Hemoglobin (Anemia)	Regression, highest external $R^2 = 0.61$	Clinical Measurement
Mitani et al. [30]	Color Fundus	Inception-v4	57,163 images	Random split	Not Mentioned	Hemoglobin (Anemia)	AUROC 0.87	Clinical Measurement
Chen et al. [31]	OCT	LDA	571 images	Leave-one-out cross-validation	Not Mentioned	Hemoglobin (Anemia)	Accuracy 0.84	Biochemical Testing
Jain et al. [20]	Palpebral Conjunctiva	SVM, CNN	601 augmented images	Random split	Not Mentioned	Hemoglobin (Anemia)	Accuracy 0.97, Sensitivity 0.99, Specificity 0.95	Not Reported
Chen et al. [32]	Palpebral Conjunctiva	SVM, ANN	50 images	10-fold cross-validation	Not Mentioned	Hemoglobin (Anemia)	SVM: Sensitivity 0.78, Specificity 0.83; ANN: Sensitivity 0.75, Specificity 0.83	Biomedical Testing

TABLE 4: Comparison of works on anemia

ANN, Artificial Neural Network; AUROC: Area Under the Receiver Operating Characteristic Curve; CNN, Convolutional Neural Network; LDA, Linear Discriminant Analysis; OCT: Optical Coherence Tomography; SVM, Support Vector Machine

Furthermore, Chen et al. [31] proposed an automatic anemia screening method based on images of retinal vascular OCT. They demonstrated gradient and threshold algorithms for ROI extraction and enhanced region-growing algorithms based on adaptive seed points for segmenting blood vessels. Before feature extraction, they also statistically studied the association between hemoglobin content, intravascular brightness, and vascular shadow in OCT images. The proposed approach had an accuracy of 0.84, indicating clinical potential for screening for anemia. On the other hand, Chen et al. [32] used the color distribution of the conjunctiva of the eyelids to diagnose anemia. The research was designed in two phases: In the first phase, a thresholding decision technique based on the high hue rate feature was used, and in the second step, a minimum distance classifier based on Mahalanobis distance was applied to the

middle pixel value. A support vector machine or an artificial neural network was used for the classification.

For anemia, very little research has been conducted, and most research did not make any external validation. So, before using it in the real-life hospitals, the research should be externally validated.

Eye as a Biomarker for the Detection of CVD

The eye is such an organ that it can be used for non-retinal diseases like systemic diseases due to its non-invasive technique. In contrast to the majority of other organs, the eye's retina allows for direct optical imaging of blood vessels and neural tissue without the need for surgical or radiological intervention. Additionally, changes in the retina's structure, color, and vasculature are frequently early indicators of systemic conditions, such as cardiovascular, renal, neurological, and hematologic. This transforms retinal image analysis into a powerful and easily accessible tool for the early detection of a wide range of non-ocular diseases. To predict CVD risk, physicians have done fundus examinations on hypertensive patients for over a century to determine the extent and degree of retinal vascular damage [67]. This study is predicated on the idea that alterations detected in the retinal vasculature, such as the degree of retinal arteriolar narrowing, reflect vascular disease in peripheral, cerebral, and coronary blood vessels and may indicate CVD risk [68]. Systolic and diastolic BP, hypertension, retinal vessel caliber, coronary artery calcium (CAC), and carotid artery atherosclerosis are cardiovascular parameters that can be predicted from RFP [33]. Age, sex, and ethnicity are non-modifiable risk factors for CVD events; modifiable risk factors include diabetes [69], hypertension [70], hyperlipidemia [71], and smoking [72].

Vaghefi et al. [34] demonstrated that the proposed deep learning algorithm CVD-AI, using a retinal image as the only input, could assess both the 10-year probability of a person experiencing a cardiovascular event (hypertensive retinopathy [HR]) and the relative components from which this risk score was created. They generated a CVD risk score based on the CVD-AI model using 110,272 fundus pictures from a database of 55,118 patients. The effectiveness of the prediction methods was then determined by comparing the results with the actual rate of cardiovascular events [34]. A precolonial indicator of atherosclerosis, CAC, is highly correlated with the likelihood of developing clinical CVD [73]. International recommendations increasingly use clinical risk prediction models and CAC score measurement to stratify CVD risk [74]. Based on the predicted CAC of deep learning, Rim et al. [29] created and validated a new cardiovascular risk stratification method and obtained a predicted score (RetiCAC) from retinal images. The three-tier CVD risk stratification approach, developed using RetiCAC and cardiac CT scans, was performed to predict future CVD events [28]. Therefore, this study implied that RFP, a non-radiation-based imaging modality for cardiovascular risk stratification in low-resource settings, could be more practical than cardiac CT. Son et al. [35] evaluated a high accumulation of CAC in 44,184 images of the retinal fundus with deep learning (inception-v3) for the discrimination of no CAC from CACS >100 and achieved an AUROC of 0.82. Furthermore, Chang et al. [33] developed a deep -learning model that predicted atherosclerosis using images of the retinal fundus and validated its clinical implications through a retrospective cohort study. Poplin et al. [36] developed algorithms to predict the beginning of significant adverse cardiovascular events during the next five years. The AUC for the RFPs, 0.7, was comparable to the AUC for the European Systematic Coronary Risk Evaluation, 0.72. They predicted cardiovascular risk factors not previously believed to be present or quantifiable in retinal pictures, including age, gender, smoking status, systolic BP and significant adverse cardiac events. A set of previous studies on CVD and comparative analysis is shown in Table *5*. Recently, Araki et al. [37] analyzed the coronary layered plaque using a Visual Transformer-based deep learning algorithm and achieved 77.6% accuracy. In this study, OCT images were used for training and external validation. So, the layered technique would help the cardiac event. The total number of research studies is also small, and when the dataset size decreases, the model performance also decreases. So, further research is needed to make the model more robust and practically useful.

Paper	Input	AI Structure/Other Method	Dataset Size	Type of Internal Validation	External Validation	Disease Covered	Outcomes	Reference Standard
Vaghefi et al. [34]	Fundus images	Inception-ResNet-V2/ResNet50	UK Biobank (95,992 images)	Random split	AREDS-1 dataset (14,280 images)	CVD	4.9% [IQR 2.9–8%] vs. 2.3% [IQR 1.3–4.3%], P < 0.01	Not Mentioned
Rim et al. [29]	Fundus images	EfficientNet	8,930 images	Random split	Not Mentioned	Coronary artery calcification	AUC 0.74, 95% CI (0.73–0.75)	Expert grades (cardiac CT)
Son et al. [35]	Fundus images	Inception-v3	44,184 images	5-fold cross-validation	Not Mentioned	Coronary artery calcification	AUROC 0.82	Expert graders (cardiac CT)
Chang et al. [33]	Fundus images	Xception	15,408 images	Random split	Not Mentioned	Carotid artery atherosclerosis	AUROC 0.71, Accuracy 0.90, Sensitivity 0.89, Specificity 0.40	Expert consensus (ultrasonography)
Poplin et al. [36]	Fundus images	Inception-v3	24,008 (UK Biobank) + 1,958 (EyePacs)	Random split	12,026 and 999 patients (independent sets)	Cardiovascular risk factors	AUC 0.97	Biochemical testing, clinical measurement, questionnaire
Akari et al. [37]	OCT images	Vision Transformer (ViT)-based DL	237,021 OCT images (581 patients)	5-fold cross-validation	65,394 images (292 patients)	Coronary layered plaque progression	AUC 0.86, Sensitivity 0.77, Specificity 0.76, Accuracy 0.78	Not Mentioned

TABLE 5: Comparison of works on coronary artery disease

AUROC, Area Under the Receiver Operating Characteristic Curve; AUC, Area Under the Curve; CVD, Cardiovascular Disease; CT, Computed Tomography; DL, Deep Learning; IQR, Interquartile Range; OCT, Optical Coherence Tomography

Eye as a Biomarker for the Detection of Chronic Kidney Disease

Deep learning algorithms may be practical for routine screening to detect prevalent chronic diseases, such as kidney disease, in remote or resource-limited places. Very few studies and experiments in the scientific community have attempted to diagnose chronic kidney disease (CKD) from retinal images.

Paper	Input	AI Structure/Other Methods	Dataset Size	Type of Internal Validation	External Validation	Disease Covered	Outcomes	Reference Standard
Zhang et al. [38]	Fundus images, age, gender, height, weight, BP	ResNet-50	115,344 images	Random split	8,059 patients (CC-FII-C) + 3,081 (COCAS cohort)	CKD, Type-2 diabetes	AUROC 0.93	Biochemical Testing
Rim et al. [29]	Fundus images	VGG16	236,257 images	Not Mentioned	Not Mentioned	Gender, body compositions, creatinine, BP, hematological parameters	AME 0.11 (95% CI 0.11–0.11), R^2 = 0.38 (0.37–0.40)	Not Mentioned
Sabanayagam et al. [17]	Retinal fundus images, age, sex, ethnicity, diabetes, hypertension	CondenseNet	5,188 patients (training), 1,297 (validation)	Random split	3,735 patients (Singapore study) + 1,538 (Beijing Eye Study)	CKD	External AUROC 0.83–1.00	Biochemical Testing
Kang et al. [39]	Color fundus images	Custom Deep Learning Model	25,706 images	Not Mentioned	Not Mentioned	CKD	AUC 0.81	Not Mentioned

TABLE 6: Comparison of works on chronic kidney disease

AUC, Area Under the Curve; AUROC, Area Under the Receiver Operating Characteristic Curve; BP, Blood Pressure; CKD, Chronic Kidney Disease

A set of previously done studies about CKD and the comparative analysis are shown in Table *6*. Zhang et al. [38] utilized 115,344 retinal fundus photographs from 57,672 individuals in conjunction with clinical metadata (age, gender, height, weight, body mass index, and BP) to detect CKD. After training a deep learning model, ResNet50, they discovered an impressive result with an AUC score between 0.85 and 0.9 for various input conditions. After capturing photos of 8,059 patients from the CC-FII-C cohort and 3,081 from the COCAS cohort and undergoing external validation, they also built a system to take retinal images and identify CKD. It is stated that biochemical testing was employed as a reference standard to detect CKD in patients. As little more than a result, Rim et al. [29] attempted to establish the eye as a biomarker by training three different datasets with 236,257 photos to predict 47 outcomes (gender, body composition, creatinine, BP, hematological parameters, etc.) and achieved success with t10 components. Among the 47 outcomes, there was one for creatinine levels; this study differs from others. Other articles attempted to classify CKD, whereas this one attempted to predict the amount of creatinine. After training the VGG16 deep neural network model, the evaluation outcomes were AME 0.11 and R^2 0.38 (0.37 to 0.4). This study used deep learning to predict systemic indicators, such as body composition indices and blood creatinine, in groups of individuals with the exact same ethnic origin from retinal scans.

Sabanayagam et al. [17] also trained deep learning models and used a 5-block CondenseNet-based model with 5,188 patient data (in addition to segregating 1,297 patient data for validation). They trained the models in three distinct categories: first, using simple images; second, using images to train with risk factors such as age, gender, race, diabetes mellitus status, and hypertension; and third, combining the risk factors and images to create a deep learning model. After training, the models acquired AUROC values between 0.81 and 1. Using a deep learning model, Kang et al. [39] organized 25,706 retinal fundus pictures from 6,212 patients to diagnose CKD. After model training, an AUC value of 0.81 was found.

Eye as a Biomarker for the Detection of Hypertension Disease

Hypertensive retinopathy (HR) is a change in the retina's tiny blood vessels that might indicate blood vessel damage brought on by high BP. There are three main stages of HR: exudative, with retinal microaneurysms, hemorrhages, hard fluid, and cotton-wool spots; sclerotic, with focal arteriolar narrowing, arteriolar wall opacification and compression of the venules; and vasoconstrictive, with generalized narrowing of the retinal arteries [5]. Between 4% and 18.7% of the general population who do not have diabetes are affected by HR. This condition affects more men than women [5]. In the research [5], the meta-analysis revealed that both mild and moderate HR are independent risk factors for CVD events. Although mild HR may be associated with modestly increased risk, the clinical implications of these findings remain unclear. By integrating a pre-trained model and dense blocks, Sajid et al. [21] developed Mobile-HR, a light system for diagnosing eye diseases related to HR. Nine thousand one hundred seventy

retinal fundus images were collected from Pakistani hospitals for analysis, and color space was tailored to how individuals perceive colors. They proposed an automated system for identifying HR diseases with 0.99 accuracy. However, it is limited by a small dataset and does not evaluate the five classes of HR.

Paper	Input	AI Structure/Other Method	Dataset Size	Type of Internal Validation	External Validation	Disease Covered	Outcomes	Reference Standard
Zhang et al. [40]	Fundus images	Inception-v3	625 images	Random split	Not Mentioned	Hypertension	AUROC 0.766	Clinical Measurement
Dai et al. [41]	Fundus images	U-Net, CNN	1,419 images	5-fold cross-validation	Not Mentioned	Hypertension	Accuracy 0.61, Mean AUROC 0.65	Clinical Measurement
Sajid et al. [21]	Fundus images	Mobile-HR, MobileNet, SVM	9,170 images	10-fold cross-validation	Not Mentioned	Hypertension	Accuracy 0.99, Sensitivity 0.99, Specificity 0.99, AUC 0.99	Clinical Measurement

TABLE 7: Comparison of works on hypertension disease

AUC, Area Under the Curve; AUROC, Area Under the Receiver Operating Characteristic Curve; CNN, Convolutional Neural Network; SVM, Support Vector Machine

Hypertension, hyperglycemia, and dyslipidemia are characterized by direct measurements of BP, plasma glucose, and triglyceride levels, respectively. The relative effects of these conditions are among the key risk factors for CVD, the leading worldwide cause of morbidity and mortality [40,75]. Based on retinal fundus images, Zhang et al. [40] created automated AI models that may be utilized for extensive population screening and predict high BP, high blood sugar, dyslipidemia, and other CVD risk factors. The models in this research could predict hyperglycemia with an AUROC of 0.88, hypertension with 0.77, and dyslipidemia with 0.7. Also, these models can predict from blood tests several erythrocyte properties, such as hematocrit, mean corpuscular hemoglobin concentration, and a group of CVD risk variables, with an AUC of >0.7. A set of previously done studies about hypertension and the comparative analysis are shown in Table 7.

Dai et al. [41] researched the East Asian population to investigate how hypertension affects the morphological characteristics of the retinal microvasculature. This study employed a deep learning technique that can recognize subclinical traits visible below the threshold of a human observer. They extracted interference information other than retinal vasculature from 2012 retinal images and used only morphological data regarding blood vessels. With training, the CNN model's classification accuracy was 0.61. Heat maps for the class "Hypertension" were created using gradient-weighted class activation mapping. For CKD analysis, we found only three research studies and only one externally validated article, so there are lots of scopes to extend this area more deeply.

Eye as a Biomarker for the Detection of Age and Gender

The retina is the sole organ in the body that allows for noninvasive simultaneous visualization of neuronal and vascular tissue [11]. Additionally, it is becoming more widely acknowledged that retinal biomarkers may successfully correlate with systemic indicators of healthy aging and disease. Table *8* shows a set of previously done studies about age and gender and the comparative analysis.

Paper	Input	AI Structure/Other Method	Dataset Size	Type of Internal Validation	External Validation	Covered Area	Outcomes	Reference Standard
Korot et al. [42]	Fundus images	CNN	84,743 images	Random split	Moorfields Eye Hospital (252 images)	Gender	Sensitivity 0.84, Specificity 0.72, PPV 0.78, Accuracy 0.79	Demographics
Munk et al. [43]	Fundus images + OCT	CNN	13,566 fundus + 8,554 OCT images	Random split	Not Mentioned	Age, Gender	AUC: Fundus 0.80, OCT cross-sections 0.84, OCT volumes 0.90	Demographics
Gerrits et al. [44]	Fundus images	MobileNet-V2	2,400 images	Random split	Not Mentioned	Age, Gender	Age: MAE 2.78 years; Gender: AUC 0.97	Biochemical testing, clinical measurements, questionnaires
Kim et al. [45]	Fundus images	CNN	192,724 images	Random split	Not Mentioned	Age, Gender	AUC 0.96	Demographics
Yamashita et al. [46]	Fundus images	Logistic Regression	112 images	Leave-one-out cross-validation	Not Mentioned	Gender	AUC 0.97	Demographics
Khalifa et al. [22]	External eye images	CNN	3,000 augmented images	Random split	Not Mentioned	Gender	Accuracy 0.99	Demographics
Poplin et al. [36]	Fundus images	Inception-v3	24,008 (UK Biobank) + 1,958 (EyePacs)	Random split	12,026 and 999 patients (independent sets)	Age, Gender	AUC 0.97	Biochemical testing, clinical measurements, questionnaires

TABLE 8: Comparison of works on age and gender

AUC, Area Under the Curve; CNN, Convolutional Neural Network; MAE, Mean Absolute Error; OCT, Optical Coherence Tomography; PPV, Positive Predictive Value

Korot et al. [42] developed a deep learning framework that physicians can use without coding to predict gender from retinal fundus images. They experimented on the UK Biobank dataset containing 84,743 retinal fundus photos. The area of the code-free deep learning model under the receiver operating characteristic curve for internal validation was 0.93. This implies that a code-free framework might be comparable to cutting-edge algorithms created by programmers for related jobs. Munk et al. [43] employed retinal fundus pictures and OCT scans to predict patient information such as age or sex. They observed that algorithms based on deep learning could categorize the patient's sex and age from color fundus photography and OCT for a wide range of patients, regardless of underlying disease or image quality. The eye fovea and optic disc must be visible for non-random sex determination to be achievable using fundus imaging.

Gerrits et al. [44] examined whether fundus pictures can predict cardiometabolic risk factors using the Qatar Biobank dataset containing retinal scans from 3,000 Qatari citizens. Individual-level predictions were generated by merging information from an optic disc-centered and a macula-centered image of both eyes with deep learning models utilizing the MobileNet-V2 architecture. When trained for testosterone, they discovered that deep learning models indirectly predict sexual orientation.

In contrast, Kim et al. [45] wanted to evaluate CNN models that predict age and sex from retinal fundus images in normal subjects and in participants with an underlying systemically vascular altered state.

The human retina and the optic disc undergo ongoing alterations due to aging and share physiological or pathological characteristics with the brain and systemic vascular state. In this study, CNN age and sex prediction models were developed using 219,302 fundus images from regular participants without hypertension, diabetes mellitus, or smoking. The CNN model accurately predicted the age of regular participants; the correlation between the predicted age and chronological age was R^2 0.92. Yamashita et al. [46] endeavor to comprehend what characteristics were recognized by algorithms as helpful in gender prediction. In several traits related to sex, such as the papillomacular angle, the tessellation fundus index,

the angles of the retinal vessel, and the trajectory of the retinal artery, logistic regression was performed.

This study, the only one to use gender-specific logistic regression models, obtained an AUROC of 0.78. Using a deep CNN and 3,000 iris images, Khalifa et al. [22] classified gender. The suggested design uses graph-cut segmentation to separate the iris from a background image. The proposed model has 16 additional layers, the first three of which are convolutional layers to extract features with various convolution window sizes. The latter three levels are fully connected layers for classification, with a 0.99 accuracy rate. Poplin et al. [36] attempted to use deep learning to predict cardiovascular risk factors such as age, gender, smoking status, systolic BP, and major adverse cardiac events from retinal fundus images. They demonstrated how the trained deep learning algorithms used anatomical elements like the optic disc or blood vessels to provide each prediction.

Eye as a Biomarker for the Detection of Diabetes

Diabetes has been the subject of the most significant research into diagnosing retinal pictures using machine learning and deep learning algorithms. Examinations include fundus, OCT, infrared iris, and OCT angiography images.

Paper	Input	AI Structure/Other Method	Dataset Size	Type of Internal Validation	External Validation	Disease Covered	Outcomes	Reference Standard
Samant et al. [47]	Infrared iris images	Random Forest	338 images	10-fold cross-validation	Not Applicable	DR Detection	Accuracy 0.90, Specificity 0.97, Sensitivity 0.99	Biochemical Testing
Aslam et al. [48]	OCTA	Random Forest	152 images	Leave-one-out cross-validation	Not Applicable	DR Detection	AUC 0.80, Specificity 0.49	Biochemical Testing
Saha et al. [18]	Color fundus images	CNN	7,000 images	Random split	Not Applicable	DR Detection	Accuracy 1.00, Sensitivity 1.00, Specificity 1.00	Clinical Trial
Lam et al. [49]	Color fundus images	CNN	36,200 images	Random split	400 images	DR Detection and Staging	Accuracy 0.75	Not Mentioned
Hsieh et al. [52]	Color fundus images	CNN + Inception-V4	39,136 images	Random split	1,875 images	DR Detection	Accuracy 0.98	Clinical Assistance
Rêgo et al. [54]	Color fundus images	CNN + Inception-V3	350 images	Not Mentioned	Not Mentioned	DR Detection	Sensitivity 0.81, Specificity 0.96, PPV 0.78, NPV 0.96	Not Mentioned
Zang et al. [55]	OCT/OCTA	3D CNN	456 images	5-fold cross-validation	Not Mentioned	DR Detection	rDR Classification AUC 0.96, vtDR Classification AUC 0.92	Clinical
Elgafi et al. [60]	OCT	DNN	188 images	5/10-fold + LOSO cross-validation	Not Mentioned	DR Detection	Accuracy 0.97	Not Mentioned
Dai et al. [57]	Color fundus images	ResNet	466,247 images	Random split	209,322 images	DR Detection	AUC: Mild 0.94, Moderate 0.96, Severe 0.96, Proliferative 0.97	Not Mentioned
Oh et al. [58]	Ultra-widefield fundus images	ResNet-34	13,271 images	10-fold cross-validation	Not Mentioned	DR Detection	Accuracy 0.83, AUC 0.92	Clinical
Gargeya et	Fundus	CNN	75,136	5-fold cross-validation	MESSIDOR 2 + E-	DR Detection	AUC 0.97, Sensitivity 0.94,	Expert

al. [63]	images		images		Ophtha databases		Specificity 0.98	Consensus
Hacisoftaoglu et al. [23]	Fundus images	ResNet50	52,401 images (6 datasets)	Single/crossed/merged dataset	Not Mentioned	DR Detection	Accuracy 0.99, Sensitivity 0.98, Specificity 0.99, AUC 0.99	Not Mentioned
Heisler et al. [59]	OCT/OCTA images	VGG19 + ResNet50 + DenseNet	463 volumes (380 eyes)	Random split	Not Applicable	DR Detection	Accuracy 0.92	Expert Consensus
Bhuiyan et al. [56]	Fundus images	Xception + Inception-v3 + Inception-ResNet-v2 + LMT	88,702 images	Random split	264 images	DR Detection	AUC 0.99, Sensitivity 0.99, Specificity 0.98	Not Mentioned
Mohamed et al. [53]	Color fundus images	PCA + CNN	80,000 images	Random split	100 images	DR Multi-class Detection	Accuracy 0.85, Sensitivity 0.89, Specificity 0.96	Not Mentioned
Wang et al. [64]	Color fundus images	LesionNet	12,252 images	Random split	565 images	Referable DR Identification	AUC 0.94, Sensitivity 0.91, Specificity 0.81, F1-score 0.85	Expert Consensus
Alyoubi et al. [50]	Color fundus images	CNN299 + CNN512	DDR (13,673) + APTOS (3,662)	Random split	Not Applicable	DR Classification	Accuracy 0.89	Not Mentioned
Bellemo et al. [51]	Fundus images	Ensemble AI (VGGNet + Residual NN)	76,370 images	Random split	Not Mentioned	Referable/Vision-Threatening DR Screening	AUC 0.97, Sensitivity 0.92, Specificity 0.89	Not Mentioned
Jacoba et al. [61]	Handheld retinal images	Deep Learning	17,829 images	Random split	Not Mentioned	DR Classification	AUPRC 0.99, Sensitivity 0.96, Specificity 0.98	Not Mentioned
Silva et al. [62]	UWF retinal images	Automated ML + Statistical Analysis	1,179 images	Random split	Not Mentioned	DR Progression	AUPRC 0.86, Sensitivity 0.80, Specificity 0.72	Not Mentioned

TABLE 9: Comparison of works on diabetes disease

AUC, Area Under the Curve; AUPRC, Area Under the Precision-Recall Curve; CNN, Convolutional Neural Network; DNN, Deep Neural Network; DR, Diabetic Retinopathy; LOSO, Leave-One-Subject-Out; ML, Machine Learning; NN, Neural Network; NPV, Negative Predictive Value; OCT, Optical Coherence Tomography; OCTA, Optical Coherence Tomography Angiography; PCA, Principal Component Analysis; PPV, Positive Predictive Value; rDR, Referable Diabetic Retinopathy; UWF, Ultra-Widefield Imaging; vtDR, Vision-Threatening Diabetic Retinopathy

A variety of AI methods have been applied, including machine learning techniques like random forests and numerous deep learning models (CNN, Inception-V4, Inception-V3, DCNN, ResNet, ResNet-34, ResNet-50, VGG19, DenseNet, Xception, LessionNet, CNN299, and CNN512). A set of previous studies on DR and the comparative analysis is shown in Table *9*. Samant and Agarwal [47] and Aslam et al. [48] employed random forest to classify infrared iris and OCTA images of diabetic and nondiabetic patients, respectively. Samant's work utilized a larger dataset (338 images) than Aslam's dataset (152 images), and the performance of the algorithm indicates that the former achieved a better result (accuracy 0.8963, specificity 0.9687, and sensitivity 0.988) than the latter (AUC 0.8, specificity 0.49). Although both experiments utilized the same technique with varying image kinds and dataset sizes, the performance may depend on the dataset size.

Saha et al. [18] achieved the highest assessment scores, with 100% accuracy, sensitivity, and specificity; they trained a deep CNN using 7,000 color fundus images. Lam et al. [49], on the other hand, trained a CNN model on 36,200 images but reported the lowest performance among all studies, with accuracies of 0.75, 0.69, and 0.57 for binary, ternary, and quaternary classification models, respectively. Several studies employed CNN architectures [18,49-55], with the highest and lowest scores both derived from CNN models. Hsieh et al. [52] reported an accuracy of 0.98 using Inception-V4; Rêgo et al. [54] achieved a

sensitivity of 0.8, specificity of 0.96, positive predictive value of 0.78, and negative predictive value of 0.96 with Inception-V3; and Bhuiyan et al. [56] scored an AUC of 0.99, sensitivity of 0.99, and specificity of 0.98. The ResNet model was also widely used and demonstrated excellent results; for example, Dai et al. [57] used a ResNet-based algorithm called DeepDR and obtained AUC scores of 0.94, 0.96, 0.96, and 0.97 across various datasets. Oh et al. [58] used ResNet-34 and obtained an accuracy of 0.83 and an AUC of 0.92. Hacisoftaoglu et al. [23] used ResNet50 and achieved an accuracy of 0.97, sensitivity of 0.98, specificity of 0.99, and an AUC of 0.99. Heisler et al. [59] also used ResNet50 and achieved accuracies of 0.92 and 0.9 for two different settings. Some other models were also used, such as Elgafi et al. [60], who used a deep neural network and achieved an accuracy score of 0.97. Heisler et al. [59] used DenseNet with VGG19 and ResNet-50. Wang et al. [39] used LessionNet and obtained an AUC score of 0.94, a sensitivity of 0.91, and a specificity of 0.81. Bellemo et al. [51] used an ensemble model containing one VGGNet and one residual neural network architecture and obtained an AUC of 0.97, sensitivity of 0.92, and specificity of 0.89. Jacoba et al. [61] used a handheld retinal camera to take the retinal images and analyze the DR classification. They also validated it with internal and external datasets. They achieved 97% accuracy in internal validation and external validation. AutoML models were developed using previously obtained handheld retinal pictures from five regions: macula-centered, disc-centered, superior, inferior, and temporal macula. Each image was annotated according to the International Diabetic Retinopathy and Diabetic Macular Oedema Classification Scale by four certified graders at a centralized reading facility supervised by a senior retina specialist in a recent study [62] from 2024 that used ultra-wide field retinal images to predict DR progression. Here, 1,179 images were used with mild or moderate nonproliferative DR (NPDR) for 3 years of longitudinal follow-up retinal imaging. Fifty-one percent (590 out of 1,179) of the training set had DR advancement. For baseline mild NPDR, the model's Area Under the Precision-Recall Curve was 0.72; for moderate NPDR, it was 0.86. On the validation set, the following values were recorded for eyes with mild NPDR: sensitivity: 0.72 (95% CI, 0.57-0.83), specificity: 0.63 (95% CI, 0.57-0.69), prevalence: 0.15 (95% CI, 0.12-0.20), and accuracy: 64.3%. For eyes with moderate NPDR, the corresponding values were 0.80 (95% CI, 0.7-0.87), specificity: 0.72 (95% CI, 0.66-0.76), prevalence: 0.22 (95% CI, 0.19-0.27), and accuracy: 73.8% on the validation set.

Let us analyze the dataset size (which contains various retinal scans). We can observe that some research used a limited number of images while others utilized a considerable number. Frequently, models' performance depends on the number of photos, particularly in machine learning models; deep learning models also scored somewhat worse with fewer images. However, nearly all models perform well when many photos are utilized. Consequently, performance is not model-dependent but entirely data-size-dependent.

Most of the research conducted internal validation using k-fold cross-validation or random split. However, only a few of them performed random tests using external data, and those datasets were of tiny size. In addition, only a minority of studies consult domain experts throughout their experiments.

The Role of AI Models in Diagnosing Eye Diseases

The precise identification and distinguishing diagnosis of ocular disorders represent unresolved medical needs to establish appropriate therapeutic interventions and healthcare measures to manage the visual condition and mitigate its detrimental consequences effectively [76]. AI has played a significant role in detecting not only non-eye systematic diseases but also eye diseases, i.e., glaucoma, cataracts, retinopathy of prematurity, keratoconus, macular edema, conjunctivitis, etc. [77,78]. Many techniques have been used to diagnose eye diseases, including CNN, image segmentation, transfer learning, visual field analysis, ensemble methods, explainable AI, online screening with telemedicine, and mobile application-based screening. Using various forms of convolutional and recurrent neural networks, it is possible to identify ocular surface diseases such as pterygium, keratoconus, infectious keratitis, and dry eye [77,79]. Ultrawide field fundus/color fundus imaging and OCT/OCTA images are widely used imaging technologies for AI-based diagnosis [80]. Moreover, other types of images, such as fluorescein angiography, indocyanine green angiography, scanning laser ophthalmoscopy, wide-field imaging, fundus autofluorescence, microperimetry, etc. [81], have been used. Overall, it is said that AI is a significant tool for diagnosing and recognizing eye diseases, and right now, ophthalmologists always get help from AI for eye treatment.

Publicly Available Related Datasets

We have also searched for publicly available retinal image datasets for further research. However, we have found that only a few datasets are publicly available, except for DR. Table *10* presents a brief description of the dataset. For Alzheimer's disease, there is only one publicly available dataset, SD-OCT [82], which contains AD and healthy controls OCT images. Next, two datasets for anemia disease are available: CHASE-DB [83] and DRIVE [84]. No public dataset is available for coronary artery and CKD, but some private datasets are available and are available on request for specific purposes. There are also two datasets available for hypertension: DR HAGIS [85] and BiolmLab [86]. For diabetic disease, most of the public datasets are available: DRCR.net [87], EyePACS [88], Messidor [89], DRIVE [84], and DIARETDB [90]. For the sex prediction, there is a large dataset, SEEDS [91], which contains 172,170 fundus images of 9,956 persons. Other types of images are used for different purposes.

Disease Name	Dataset Names	Description
Alzheimer's Disease	SD-OCT [92]	Retinal images of Alzheimer's patients and healthy individuals.
Anemia	CHASE-DB [83]	Contains retinal vessel segmentation data relevant to anemia detection.
	DRIVE [84]	Includes abnormal retinal vessel segmentation data linked to anemia.
Coronary Artery Disease	No public dataset available	NA
Chronic Kidney Disease	No public dataset available	NA
Hypertension Disease	DR HAGIS [85]	Fundus images showing retinal vessel segmentation across four disease types.
	BioImLab [86]	60 retinal vessel images from normotensive and hypertensive patients.
Diabetes Mellitus	DRCR.net [87]	Images of diabetic macular edema and retinopathy.
	EyePACS [88]	~5 million diabetic retinopathy images.
	Messidor [89]	Normal/abnormal retinal images for diabetic retinopathy detection.
	DRIVE [84]	Retinal vessel segmentation dataset for diabetes analysis.
	DIARETDB [90]	Fundus image collection for diabetic retinopathy detection.
Age and Gender	SEEDS (Singapore Epidemiology) [91]	172,170 fundus images from 9,956 individuals aged 40+ (retrospective cross-sectional analysis).
Others	ROPIDB [93]	Retinopathy images in premature infants with vascular abnormalities.
	TREND [94]	Defines normal retinal anatomy/microvascular geometry via portable fundus camera.

TABLE 10: A brief representation of publicly available related datasets

Limitations, difficulties, and future challenges

Areas of Improvement

Medical examinations eventually place a more significant financial strain on society. Unfortunately, more medical diagnostic tools are needed for this increasing population. Utilizing a single diagnostic tool for multiple diseases will make it easier to handle resource constraints. While AI-based ocular imaging offers promising prospects, there are still significant issues to address. Using ophthalmic images and AI, we have found much potential for diagnosing stress, hypertension, Alzheimer's disease, anemia, CVD, and chronic diseases. Most conventional diagnostic techniques require time-consuming blood tests. There is currently no fast test for many common diseases. Their size and weight make medical equipment challenging to transport in dangerous conditions. The standard laboratory approach requires a variety of symptom analyses and tests to detect hypertension and CVD. The most frequent cause of unexpected mortality under challenging conditions is cardiac arrest.

We have identified several existing work limitations from our reviewed papers. The research studies we have collected show that most of the studies lack external validation, which is essential for building reliable and general AI models. The current research has investigated neither OCT-based kidney disease nor hypertension prediction systems. Eye movement measurements can be used to identify mental stress. However, there is a need for more studies utilizing retinal images and AI. Currently, there is no research examining the ability of AI ophthalmic imaging algorithms to stage the severity of systemic disease or detect longitudinal changes in systemic disease.

Additionally, several systemic disorders produce similar effects on ocular structures, such as the retina and choroid. If multiple diagnostic tasks are assigned to the AI model simultaneously without identifying specific feature patterns for each condition, there is a risk of false positive diagnoses. Although some studies have attempted to incorporate broader systemic illness screening tasks into general AI systems, further research is needed to effectively differentiate between various diagnostic tasks.

Challenges

Various challenges exist to establishing the eye as a biomarker as AI becomes increasingly integrated into

medical practice. The first is that it requires interdepartmental collaboration. However, systemic parameters are not always necessary for management in ophthalmology clinics, and images must be retrieved independently. The second is that the public dataset is less available, and retinal image acquisition is costly. Validation is another challenge in this area. Large-scale research involving a variety of populations is necessary for validation, as are longitudinal studies to evaluate the predictive power of biomarkers. The fourth challenge is ensuring that the ocular biomarkers are sensitive and specific enough to identify changes in disease progression or treatment response.

Verifying that they are unaffected by other influences necessitates the careful selection of biomarkers and extensive testing. Making eye biomarker tests affordable and accessible to patients is the fifth limitation. The cost of biomarker testing may hinder its frequent use in clinical practice. Due to genetic distinctions, eye-related biomarkers can vary across different ethnic groups and individuals. This makes it challenging to establish universal biomarkers applicable to all populations. Moreover, not all healthcare facilities or geographical regions can offer biomarker testing, limiting patient access. Additionally, there are some limitations to our systematic review. AI research is rapidly evolving, with new developments emerging daily. It is important to note that this study may not have included the most recent and innovative research due to the limitations of the search method employed. Specifically, studies that have not undergone peer review or have only been published in abstract form may have been overlooked.

Future Application

Next, we found fewer studies focused on HR and some publicly accessible datasets. Hence, utilizing fundus retinal images, we employed a collection of deep learning algorithms to predict hypertension. Furthermore, the causal inference-based model [95,96] can identify unseen patterns in fundus and/or OCT images that could potentially impact biomarkers used to detect non-ocular diseases. Researchers have recently been working on developing low-cost, smartphone-based fundus cameras to detect retinal diseases [97]. In the future, a novel smartphone-based eye biomarker framework could be designed as a point-of-care solution to identify early symptoms of neurodegenerative diseases, diabetes, or CVD. The smartphone-based imaging system could use AI models to capture retinal images with minimal resources and detect diseases by predicting or auto-grading plasma glucose, HbA1c, atherosclerosis, CAC, BP, triglycerides, and more.

Conclusions

The eye is a complicated organ that offers vital health information. Many eye problems, such as cataracts, glaucoma, and macular degeneration, have been discovered as biomarkers for various health illnesses, including CVD, diabetes, and neurological disorders. Modern technological advancements, like high-performance computing and neural networks, have enabled researchers to employ noninvasive imaging techniques to examine the eye and its links to chronic diseases, such as cardiovascular and brain disorders. After this systematic review, we found that diabetes, age, gender, and anemia could be diagnosed more accurately using AI techniques, and more researchers worked with them. On the other hand, research on Alzheimer's disease, coronary artery disease, CKD, and hypertension remains very limited, revealing significant gaps that need to be addressed. We have agreed with the findings, and our next goal is to complete the research gaps. Patients will find it more beneficial when disease recognition technologies are available in clinics and hospitals. Only a retinal snapshot will be enough to detect a group of chronic diseases.

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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